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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/315,298	05/20/99	TENG	C ISIS-3510

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EXAMINER	
EPPS, J	
ART UNIT	**PAPER NUMBER**
1635	5

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/315,298	Applicant(s) T ng et al.
	Examiner Janet Epps	Group Art Unit 1635

☒ Responsive to communication(s) filed on *Jun 15, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-83* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-83* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *6, 12*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Status of Claims

1. The rejection of claims 3 and 54 under 35 USC 112 first paragraph for reasons of lack of sufficient written description is withdrawn in response to Applicant's arguments. The rejection of claims 80-83 under 35 USC 112, first paragraph are withdrawn in response to Applicant's arguments. Claims 1-80 remain rejected under 35 USC 112, first paragraph for lack of enablement for the reasons set forth in the prior Office Action.

Response to Arguments

2. Regarding the rejection of claims 1-83 under 35 USC 112 first paragraph for lack of enablement, Applicants argue that the examiner has not provided sufficient reasons to establish a *prima facie* case for lack of enablement. However, the examiner's conclusion is due to the specification's failure to provide a sufficient number of working examples of the claimed invention, the breadth of the claimed invention, the unpredictability regarding the delivery and behavior of antisense oligonucleotide based therapeutics *in vivo,* and the amount of experimentation required to practice the claimed invention.

Furthermore, the specification as filed focuses on enhancing the bioavailability of oligonucleotides *in vivo,* however the claimed methods and compositions read on the therapeutic treatment of a disease in an animal. The specification as filed has not provided any evidence that their claimed compositions would be delivered to the appropriate tissues in a sufficient concentration and duration, such that the expression of a gene associated with a particular disease is modulated for

a sufficient period of time in order to produce some therapeutic benefit in an animal. Moreover, the claimed compositions and methods of use recited in claims 1-80 do not specify the sequence of the oligonucleotides useful as pharmaceutical agents, nor do they specify the nucleic molecule that is to be targeted by said oligonucleotide. Moreover, claims 1-26 do not specify the disease to be treated by the claimed pharmaceutical composition comprising an oligonucleotide. These claims read on pharmaceutical compositions comprising oligonucleotides of any particular sequence, length, modified or unmodified, to treat any animal, having any particular disease. As stated above, the specification as filed focuses on increasing the bioavailability of an oligonucleotide by varying the composition of the carrier or excipient of an oligonucleotide. There is no data provided by the specification that the claimed compositions are effective in producing any therapeutic benefit to an animal.

Additionally, there are numerous factors which produce variations in the behavior antisense oligonucleotides in a cell including the length of an oligonucleotide, modifications to the oligonucleotide, the sequence of oligonucleotide and the cell type or environment of the oligonucleotide (Crooke, 1998). Furthermore, Crooke also teaches that protein binding in general by oligonucleotides (modified or unmodified) may influence cell uptake, distribution, metabolism and excretion of the oligonucleotide. Such protein binding may produce effects that can be a mistakenly interpreted activity, and such binding may also inhibit the activity of some oligonucleotides. In addition to proteins, oligonucleotides may interact with other biological molecules, such as lipids, or carbohydrates, and such interactions, like those with proteins , will be influenced by the chemical class of oligonucleotide.

Therefore, Applicant's arguments do not take the place of evidence. Claims 1-83 remain rejected under 35 USC 112, first paragraph for reasons of lack of enablement.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 10, 12, 15, 17-18, 20, and 60-62 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

By convention there should be only one invention recited per claim. Claim 60 reads on multiple "bile salts and fatty acids", there is ambiguity as to whether the claim reads on one particular bile salt or fatty acid. Claims 61-62 recite "salts thereof', this language is also ambiguous since it is unclear if Applicants are referring to one or multiple salts thereof.

Claims 10, 12, 15, 17-18, 20 recite the following Markush language: "selected from a group consisting of..". These claims appear to claim a Markush group without the proper use of the Markush format. Alternative expressions are permitted if they present no uncertainty or ambiguity with respect to the question of scope or clarity of the claims. One acceptable form of alternative expression, which is commonly referred to as a Markush group, recites members as being "selected from the group consisting of A, B and C." See Ex parte Markush , 1925 C.D. 126 (Comm'r Pat.

1925). In addition claims 15, and 17-18 recite "selected from a group consisting of....or a mixture thereof', this Markush language is also improper since the elements of a Markush group are intended to be mutually exclusive.

Claim 79 recites "the step of orally administering", there is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> ***A person shall be entitled to a patent unless --***
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 76-79 are rejected under 35 U.S.C. 102(b) as being anticipated by Low et al.

Low et al. teach a method for enhancing transmembrane transport of exogenous molecules. The method comprises contacting a membrane of a living cell with a complex formed between said molecules and ligands selected from biotin, biotin analogs and other biotin receptor-binding ligands, and/or folic acid, folate analogs and other folate receptor-binding ligands to initiate receptor mediated transmembrane transport of the ligand complex. The method of Low et al. is used for the efficient delivery of peptides, proteins, nucleic acids and other compounds capable of modifying cell function into plant, animal, yeast, and bacterial cells. In addition, folate conjugated molecules can be used to deliver effective amounts of therapeutic agents or

pharmaceutically active agents such as oligonucleotides through parenteral or oral routes of administration to human or animal hosts (col. 4-5).

Low et al. teach each and every aspect of the instant invention thereby anticipating Applicant's claimed invention.

8. Claims 1-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Narayanan et al.

Narayanan et al. disclose pharmaceutical vehicles for delivery of oligonucleotides which include solutions, ointments, tablets, and any conventional vehicle appropriate to a given mode of delivery. A solution or ointment is preferred. A solution may include in addition to oligomers and/or salts thereof, buffers such as saline, stabilizers such as BSA and other conventional components. Ointments, creams, emulsions, lotions and shampoos all intended for topical application include well-known components. In addition, the oligomers of Narayanan are disclosed as being useful for the treatment of conditions related to cell adhesion. Narayanan et al. further teach that delivery of an effective amount of oligomer may be oral, parenteral, intravenous, or dermal or by any conventional pharmaceutical route. Conventional formulations for such administration, including an effective amount of oligomer, are part of this invention. In addition, these oligomers may be applied topically to prevent cell adhesion in target issues (col. 5-6).

Narayanan et al. teach each and every aspect of the instant invention thereby anticipating Applicant's claimed invention.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

6. Claims 80-83 are rejected under 35 U.S.C. 102(e) as being anticipated by Bennett et al. (US 6,111,094A1).

The Bennett et al. Patent discloses pharmaceutical compositions comprising an antisense oligonucleotide, wherein said composition further comprises an microemulsion, a penetration enhancer, a bile salt, a chelating agent, a surfactant, or a carrier compound. This Patent also discloses the delivery of antisense oligonucleotides by means of a rectal enema for the treatment of disorders associated with the expression of a cellular adhesion molecule. These compositions are disclosed as useful in the treatment of conditions related to the expression of a cell adhesion molecule, such conditions include Crohn's disease, inflammatory bowel disease, ulcerative colitis and undue cellular proliferation. In addition, the oligonucleotides according to SEQ ID NO: 1 and 55 are clearly disclosed as ISIS 2302 of the Bennett et al. invention.

Bennett et al. teach each and every aspect of the instant invention thereby anticipating Applicant's claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps whose telephone number is (703) 308-8883. The examiner can normally be reached on Monday through Friday from 8:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Elliott, can be reached at (703) 308-4003. The fax number for this group is (703) 305-7939.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Janet L. Epps, Ph.D.

ROBERT A. SCHWARTZMAN
PRIMARY EXAMINER

September 8, 2000